IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

HOSPIRA, INC. and ORION CORPORATION, Plaintiffs, v. EUROHEATH INTERNATIONAL SARL and WEST-WARD PHARMACEUTICAL CORP., Defendants.	)))))))))))	C.A. No. 14-487-GMS C.A. No. 14-1008-GMS

EXPERT DECLARATION OF DANIEL TALMOR, M.D., M.P.H., IN SUPPORT OF EUROHEALTH'S OPENING CLAIM CONSTRUCTION BRIEF

I, Dr. Daniel Talmor, declare as follows:

1. I am over 18 years of age and am competent to testify to the matters herein.

2. I have been retained by Goodwin Procter LLP on behalf of Eurohealth International SARL and West-Ward Pharmaceutical Corp. (collectively, "Eurohealth") and asked to provide my opinions on the meanings of certain phrases and terms used in the claims of U.S. Patent No. 6,716,867 ("the '867 patent", Exhibit A).

3. I am being compensated for my time in connection with this matter at my standard consulting rate of $500 per hour plus expenses. My compensation is not dependent in any way upon the opinions formed or the outcome of this litigation.

I. QUALIFICATIONS

4. I earned a Bachelor of Science Degree in Medical Sciences from the Ben Gurion University of the Negev in Israel ("Ben Gurion") in 1988, and an M.D. in 1993. I received my M.P.H. degree in clinical effectiveness from the Harvard School of Public Health in 2003.

5. My postdoctoral training included residencies in Cardiothoracic Surgery and Anesthesiology at Soroka University Medical Center in Israel, and fellowships in Critical Care Medicine and Cardiac Anesthesia at Beth Israel Deaconess Medical Center ("BIDMC") and Harvard Medical School. During my fellowships, I provided care for complex patients in intensive care units and operating rooms at BIDMC.

6. Following my fellowships, from 2001 through 2014, I continued to provide coverage for the intensive care units at BIDMC for not less than two weeks of every month. The patients in the BIDMC intensive care units present a full range of conditions, including patients recovering from surgery, neurosurgery, and cardiac surgery, as well as patients suffering from neurological and other serious medical diseases.

7. I am certified in Anesthesiology with a sub-specialty in Critical Care Medicine by the American Board of Anesthesiology.

8. On a weekly basis, I continue to provide care to patients in the surgical intensive care units and operating rooms at BIDMC. My clinical responsibilities include all aspects of these patients' care.

9. Since 1995, I have held multiple faculty academic appointments and leadership positions in hospitals and affiliated institutions. I am currently a professor of anesthesia at Harvard Medical School. I am also Chairman of the Department of Anesthesia, Critical Care and Pain Medicine at BIDMC. In this role, I have overall responsibility for the delivery of care in the operating rooms and in the surgical intensive care units at BIDMC.

10. In addition to my academic positions, I have served as a reviewer or editor of manuscripts submitted to various scientific journals, including the New England Journal of Medicine, Anesthesiology, and the Journal of Intensive Care. I have also authored or co-authored over 100 peer-reviewed publications and many reviews, chapters, monographs, and editorials in the fields of critical care medicine and anesthesiology. I also currently serve on the editorial boards of the journals Critical Care Medicine and Intensive Care Medicine. These are the two leading specialty journals in the field of critical care medicine.

11. I have also served on numerous regional, national, and international committees and working groups. Among many other roles, I currently serve on the Steering Committee for the U.S. Critical Illness and Injury Trials Group (USCIITG), a research consortium that coordinates and sets priorities for clinical trials relating to critically ill and injured patients. I have also served on several committees of the Society of Critical Care Medicine, including the Anesthesiology Section Steering Committee, the Disaster Planning & Response Committee, the

Research Committee, and the Anesthesiology Section Steering Committee. A copy of my curriculum vitae is attached hereto as Exhibit B.

II. MATERIALS REVIEWED AND SCOPE OF ASSIGNMENT

12. I have been asked by counsel for Eurohealth to provide my opinions regarding the meaning of certain claim terms found in the claims of the ’867 patent, as understood by the person of ordinary skill in the art. I understand that the determination of the meaning of the claim terms is referred to as “claim construction.”

13. In forming my opinions expressed in this declaration, I have reviewed the ’867 patent and the file history of the ’867 patent. I have also reviewed and considered other documents attached to this declaration as Exhibit C.

III. LEGAL STANDARDS

14. I have been informed by counsel that a claim construction analysis must be performed from the perspective of the person of ordinary skill in the art. I have been informed by counsel that this hypothetical person of ordinary skill in the art is considered to have the normal skills and knowledge of a person contributing to the field of the invention disclosed in the patent in suit at the relevant time of the invention.

15. I have been informed by counsel that to ascertain the meaning of claim terms, the specification and the file history must be considered as understood by a person of ordinary skill in the art. I understand that a person of ordinary skill in the art first looks to the words of the claim itself to define the scope of the patented subject matter, and that although words in the claim are generally given their ordinary and customary meaning, claim language is construed in light of all of the patent’s claims, specification, and file history.

16. I have been informed by counsel that claim construction involves an analysis of intrinsic evidence primarily, and then extrinsic evidence as needed. I have been informed by counsel that intrinsic evidence includes the patent's claims, specification, and file history. I have been informed by counsel that extrinsic evidence may include, for example, dictionaries.

IV. SUMMARY OF OPINIONS

17. For purposes of my analysis, I have been asked to assume that a person of ordinary skill in the art pertaining to the subject matter of the '867 patent as of April 1, 1998 would have been a physician trained in either internal medicine, general surgery, anesthesia, or pediatrics, who had obtained additional subspecialty training in critical care medicine. Such an individual would have at least several years of experience with sedation of medical and surgical patients in intensive care units.

18. In my opinion, a person of ordinary skill in the art would have understood the claim term "intensive care unit" as that term is used in claims 1 through 12 of the '867 patent to mean "any setting that provides intensive care, characterized by continuous medical supervision and intensive monitoring."

19. In my opinion, a person of ordinary skill in the art would have understood the claim term "sedating a patient in an intensive care unit" as that term is used in claims 1 through 12 of the '867 patent to mean "rendering a patient calm or asleep, and optionally treating conditions that affect patient comfort, in any setting that provides intensive care, characterized by continuous medical supervision and intensive monitoring."

20. In my opinion, a person of ordinary skill in the art would have understood the claim term "arousable and orientated" as that term is used in claims 1 through 12 of the '867 patent to mean "capable of being awakened and aware of one's surroundings."

V. OVERVIEW OF THE ’867 PATENT

21. The ’867 Patent, entitled “Use of Dexmedetomidine for ICU Sedation,” issued on April 6, 2004. I understand that the ’867 patent claims priority to two provisional applications filed on April 1, 1998 and December 4, 1998.

22. The ’867 patent is generally directed to methods of sedation of ICU patients with dexmedetomidine or pharmaceutically acceptable salts thereof. The twelve claims recite:

> 1. A method of sedating a patient in an intensive care unit, which comprises administering to the patient an effective amount of dexmedetomidine or a pharmaceutically acceptable salt thereof, wherein the patient remains arousable and orientated.
>
> 2. The method according to claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt is the sole active agent.
>
> 3. A method of sedating a patient in an intensive care unit, comprising administering a pharmaceutical composition to the patient, wherein the pharmaceutical composition comprises an active agent and an inactive agent, wherein the active agent consists of dexmedetomidine or a pharmaceutically acceptable salt thereof, and wherein the patient remains arousable and orientated.
>
> 4. The method according to claim 1, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is administered in an amount to achieve a plasma concentration of 0.1-2 ng/ml.
>
> 5. The method according to claim 4, wherein the dexmedetomidine or pharmaceutically acceptable salt thereof is administered intravenously.
>
> 6. The method according to claim 5, wherein a loading dose and a maintenance dose of dexmedetomidine are administered.
>
> 7. The method according to claim 6, wherein the patient is a human.
>
> 8. The method according to claim 7, wherein the loading dose of dexmedetomidine is 0.2-2 μg/kg.
>
> 9. The method according to claim 8, wherein the loading dose is administered in about 10 minutes.

> 10. The method according to claim 7, wherein the maintenance dose of dexmedetomidine is 0.1-2.0 μg/kg/h.
>
> 11. The method according to claim 10, wherein the maintenance dose is 0.2-0.7 μg/kg/h.
>
> 12. The method according to claim 11, wherein the maintenance dose is 0.4-0.7 μg/kg/h.

See Exhibit A.

23. The ’867 patent discloses that by administering dexmedetomidine or a pharmaceutically acceptable salt thereof to patients, they can be sedated yet remain “arousable and oriented.” ’867 Patent at col. 4, lines 49-52.

24. The ’867 patent provides three examples of the invention. Example 1 reports on the efficacy, safety and titrability of dexmedetomidine in postoperative coronary artery bypass graft(s) patients, requiring sedation in the ICU. ’867 Patent at col. 5, lines 47-49. Example 2 discloses results from a double-blind, randomized, placebo-controlled study evaluating the efficacy, safety and titrability of dexmedetomidine in mechanically ventilated patients requiring sedation in the ICU. *Id*. at col. 6, lines 35-40. Example 3 reports the results of sixteen patients from Phase III clinical trials, which were designed to evaluate the reduction in requirements for ICU sedation in patients receiving dexmedetomidine. *Id*. at col. 7, lines 44-55, col. 8, lines 48-52. The Examples of the ’867 patent report various results including Ramsay Sedation Scale results. The ’867 patent describes the Ramsay Sedation Scale as a tool to assess the sedation in experimental subjects where the level of wakefulness is scored on a scale of 1-6 based on progressive loss of responsiveness to stimuli ranging from auditory to deep painful stimuli. *Id*. at col. 4, lines 15-20.

VI. CLAIM CONSTRUCTION ANALYSIS

A. Agreed Upon Constructions

25. I have been informed that the parties agree that the term "effective amount" as used in the '867 patent means "an amount sufficient to produce the desired effect."

26. I have been informed that the parties agree that the term "patient" as used in the '867 patient means "human or animal patient."

27. I have been informed that the parties agree that the term "remains" as used in the '867 patient means "continues to be."

A. "intensive care unit"

28. I have been asked to opine regarding how the person of ordinary skill in the art would understand the claim term "intensive care unit." In my opinion, in the context of the '867 patent, a person of ordinary skill in the art reading the claims of the '867 patent in light of its specification would understand "intensive care unit" to mean "any setting that provides intensive care, characterized by continuous medical supervision and intensive monitoring."

29. The specification states that the "word intensive care unit includes any setting that provides intensive care." '867 Patent at col. 1, lines 17-18; *see also* col. 4, lines 44-45 ("The word intensive care unit encompasses any setting that provides intensive care."). Based on this language, a person of skill in the art would understand that the term "intensive care unit" as used in the '867 patent is not limited to settings in hospitals that are named "intensive care unit" (the "ICU"), but extends to other settings that provide intensive care to patients, including Emergency rooms, Post-Anesthesia Care Units, and Coronary Care Units.

30. The ICU is the unit responsible for the treatment of patients with life-threatening conditions. Most ICUs have a higher staff-to-patient ratio and access to more advanced medical resources compared to other hospital floors. The care of patients in the ICU typically involves

invasive monitoring and attention to changes in hemodynamics (including heart rate, blood pressure, cardiac output, oxygen levels), body temperature, respiration, and other measurements.

31. In other contexts in which patients receive intensive care, including Emergency Rooms, Post-Anesthesia Care Units, and Coronary Care Units, patients are subjected to or recovering from a range of circumstances, including injuries, surgical procedures, the after-effects of anesthesia, and diseases that may render their condition unstable. Patients in these settings may require sedation, mechanical ventilation, or aggressive resuscitation. Because of the potential need for these and other interventions, patients in these settings also receive continuous medical supervision and intensive monitoring.

32. I understand that Hospira has asserted that the term "intensive care unit" means "any setting that provides care to critically ill patients, typically characterized by high nurse-to-patient ratios, continuous medical supervision, and intensive monitoring." I disagree. This construction identifies a "high nurse-to-patient ratio" as a defining characteristic of intensive care. In my experience, outside of the ICU, not all settings that provide intensive care to patients have high nurse-to-patient ratios. While some state laws now mandate minimum nurse-to-patient ratios in settings that are labeled intensive care units, *i.e.* 1:1 or 1:2, nurse-to-patient ratios may be higher in other settings that provide intensive care, including emergency rooms and post-anesthesia care units, *i.e.*, 1:3 or 1:4.

33. Moreover, patients that receive intensive care in settings outside of the ICU are not always critically ill. For example, patients in Post-Anesthesia Care Units who are recovering from the after-effects of surgery and anesthesia are not necessarily critically ill, but nonetheless receive intensive care due to their need for airway management and monitoring of surgical sites and vital signs for potential post-operative complications.

B. “sedating a patient in an intensive care unit”

34. I have been asked to opine regarding how the person of ordinary skill in the art would understand the claim term “sedating a patient in an intensive care unit.” In my opinion, in the context of the ’867 patent, a person of skill in the art would understand the phrase “sedating a patient in an intensive care unit” to mean “rendering a patient calm or asleep, and optionally treating conditions that affect patient comfort, in any setting that provides intensive care, characterized by continuous medical supervision and intensive monitoring.”

35. The goal of sedation is to render a patient calm. This is typically accomplished using pharmaceuticals that put patients to sleep or relieve anxiety, and can sometimes be aided by other agents that relieve pain and discomfort.

36. In view of these practices, a person of ordinary skill in the art would understand that “sedating a patient” means rendering a patient asleep or, occasionally, awake and calm. This is consistent with the ’867 patent’s reference to the Ramsay Scale, which is depicted in Figure 1 of the patent. It describes various levels of sedation in which patients are either “asleep” (Sedation Scores 4-6) or awake and calm (Sedation Scores 2 and 3). The Examples in the ’867 patent describe sedated patients with Ramsay Scores in both of these ranges. *See, e.g.*, ’867 Patent at col. 11, lines 54-55 (“While on dexmedetomidine and intubated, she had a Ramsey [*sic*] Sedation Score of 4.”); *id.* at col. 12, lines 40-41 (“he reached the ICU with a baseline Ramsey [*sic*] Sedation Score of 4.”); *id.* at col. 9, lines 28-31 (“His Ramsay Sedation Score was 6 during the first hour . . . , then decreased to 4 and subsequently reached 3.”); *id.* at col. 10, lines 11-12 (“The patient’s Ramsey [*sic*] Sedation Score was maintained at approximately 4”).

37. In addition, as applicants stated during prosecution of the ’867 patent, a person of ordinary skill in the art would understand that sedating a patient in the context of an intensive care unit can include, but does not require, treating conditions affecting patient comfort, such as

pain. *See* Amendment dated August 9, 2002, JNT-PRECEDEX00371767-76, at 2 ("When applicants refer to 'sedation' in the context of the invention, that term is used as defined in the specification at page 1, lines 7-11; i.e., sedation *optionally* together with treatment of conditions that affect patient comfort.") (emphasis added). Applicants' use of the word "optional" reflects the understanding in the art that 1) some patients in intensive care settings who require sedation do not require treatment of pain and other conditions affecting comfort (this includes, for example, patients receiving treatment for neurological injury or a substance overdose) and 2) patients who require both sedation and pain relief are often treated with separate analgesic agents alongside sedatives (this includes patients who are sedated with dexmedetomidine).

38. I understand that Hospira has asserted that the term "sedating a patient in an intensive care unit" means "rendering a patient calm and managing patient comfort in any setting that provides care to critically ill patients, typically characterized by high nurse-to-patient ratios, continuous medical supervision, and intensive monitoring." I disagree. As discussed above, not all patients in intensive care settings who require sedation also require treatment of pain and other conditions affecting comfort.

D. "arousable and orientated"

39. I have been asked to opine regarding how the person of ordinary skill in the art would understand the claim term "arousable and orientated." In my opinion, in the context of the '867 patent, a person of skill in the art would understand the phrase "arousable and orientated" to mean "capable of being awakened and aware of one's environment."

40. I understand that Hospira has asserted that the term "arousable and orientated" means "capable of being awakened, aware of one's environment, and able to interact with others," and thus the only dispute is whether a person of ordinary skill in the art would understand the term to require that the person be able to interact with others. In my experience,

patients who are sedated are not always capable of interacting with others, even when they can be awakened and are aware of their surroundings. For example, patients under sedation who are recovering from a substance overdose may be awake and be aware of where they are, but be unable to speak coherently or understand instructions or questions from the medical staff. This is also true of patients suffering from certain types of brain injuries, including for example, patients that have had a stroke or are experiencing intracranial bleeding.

41. A person of ordinary skill in the art reading the ’867 patent would understand that not all of the patients discussed in the ’867 patent specification demonstrated the ability to interact with others. For example, several patients in the examples are described as having Ramsay Sedation Scores of 4 or higher, indicating that they were asleep. *See, e.g.*, Example 3 at col. 9, lines 28-31 (“His Ramsay Sedation Score was 6 during the first hour (baseline score, *i.e.*, the patient was fully anaesthetized after surgery), then decreased to 4 and subsequently reached 3.”); *id*. at col. 10, lines 11-12 (“The patient’s Ramsey [*sic*] Sedation Score was maintained at approximately 4.”); *id*. at col. 10, lines 44-45 (“The Ramsey [*sic*] Sedation Score was maintained at approximately 4”); *id*. at col. 11, lines 54-57 (“While on dexmedetomidine and intubated, she had a Ramsey [*sic*] Sedation Score of 4. She was calm, easily arousable, and well-oriented. She was not frightened by her surroundings (noises, personnel, and monitoring devices).”). These patients would not be able to interact with others.

I declare under penalty of perjury that the factual statements contained herein are known by me or believed by me to be correct.

DATED: August 21, 2015

____
Daniel Stuart Talmor, M.D.